REMARKS

These remarks are in response to the Office Action mailed November 12, 2008. Applicant elected the species of as species of NT agonists (i.e., NT69L) for examination on March 28, 2007. Applicant confirms this election; however, Applicant has amended claims 15, 16, and 24 to include this species for examination as a proper Markush group. Under MPEP Section 803.02, the Examiner should examine the elected species (e.g., NT69L) and if found allowable then extend the examination to other species of the Markush-type claim. The support for the amendments to claims 15-16 and 24 can be found throughout the specification and in the claims as originally filed. No new matter is believed to have been introduced.

SUMMARY OF THE DISCLOSURE

Different types of brain receptors are known to play a role in the improvement of the symptoms of certain psychiatric disease and disorders including schizophrenia. Stimulation of dopamine receptors for example by dopamine which is released from certain neurons into certain synapses between neurons produces certain symptoms, namely hallucinations (e.g., hearing voices) and paranoid delusions, termed "positive" symptoms of psychosis seen in schizophrenia. Certain drugs including amphetamines are agonists of dopaminergic receptors and stimulate these receptors. Amphetamine for example, stimulates dopamine receptors by causing dopamine containing neurons to release dopamine and by inhibit the reuptake and removal of released dopamine thus extending the duration of dopamine effects on dopamine receptors. In humans amphetamine can induce "positive" symptoms of psychosis similar to that experienced by schizophrenia patients. In animals amphetamine will produce certain behavioral effects such as a stimulation of their locomotor activity and reduces prepulse inhibition (PPI), a normal physiological phenomenon that is a measure of sensorimotor gating. Drugs that reduce the stimulation of dopamine receptors can reverse the effects of amphetamine. Investigators can identify drugs that reduce dopamine receptor stimulation by finding drugs that reverse the effects of amphetamine in animals. Such drugs would be expected to improve positive symptoms of schizophrenia

similar to "typical" or "first generation" antipsychotics. Hertel et al. and Feifel et al. teach and suggest only that NT agonists reduce stimulation of dopamine receptors.

Serotonin receptor are a distinct class of receptors from dopamine receptors and there are several types of serotonin (5-HT) receptors. The serotonin-2A receptors is one type of serotonin receptor implicated in the improvement of certain psychiatric symptoms aside from positive symptoms of schizophrenia. Serotonin released by one neuronal cell binds to and activates 5-HT2A receptors on an adjacent cell causing activation of the neuron. Reduction of stimulation of serotonin-2A receptors, either alone or in conjunction of reduction of stimulation of dopamine receptors, improves "negative" symptoms of schizophrenia, cognitive deficits seen in schizophrenia and also abnormal mood and anxiety symptoms seen in schizophrenia and other disorders such as bipolar disorder, depression and anxiety. DOI is an agonist of serotonin-2A (5-HT2A). It binds to the serotonin-2A receptor in a way similar to serotonin and produces strong activation of those receptors. Stimulation of serotonin-2A receptors can produce reduction of PPI just like stimulation of dopamine receptors, albeit by a completely different biochemical pathway. Drugs that reduce stimulation of serotonin-2A receptors reverse the PPI effects of DOI but not amphetamine. Similarly drugs that only block dopamine receptors reverse PPI effects produced by amphetamine but not DOI. Investigators can identify drugs that reduce serotonin-2A receptor stimulation by finding drugs that reverse the effects of DOI in animals. Such drugs would be expected to improve negative symptoms and cognitive deficits of schizophrenia and to improve symptoms of many other disorders such as depression, bipolar disorder and anxiety.
This is what is demonstrated by the present application, i.e., it was demonstrated that NT agonists such as NT69L and PD149163 reverse DOI-induced PPI reduction. This was a property of NT agonists not previously taught or suggest in the art.

Typical antipsychotics reverse amphetamine but not DOI induced PPI reduction. This is consistent with their known ability to strongly bind and block dopamine receptors but not serotonin-2A receptors. Typical antipsychotics are efficacious for positive symptoms of schizophrenia but not highly efficacious for negative symptoms, cognitive deficits of schizophrenia or for bipolar disorder, depression or anxiety. In contrast, "atypical" or second generation antipsychotics are

known to bind to and inhibit both dopamine and serotonin-2A receptors and these drugs, unlike typical antipsychotics, can reverse both amphetamine and DOI induced PPI effects in animals. Atypical antipsychotics are used to treat a wide variety of neuropsychiatric symptoms including negative and cognitive deficits of schizophrenia, bipolar disorder, depression and anxiety and this is mostly made possible by the fact that they modulate serotonin-2A receptors.

The ability of drug to inhibit alpha-1 receptors is also thought to be beneficial in treating psychiatric symptoms. However, this the therapeutic benefit of inhibiting alpha-1 receptors is thought to only be exhibited in the presence of existing inhibition of either serotonin-2A or dopamine receptor inhibition (augmentation effect). Investigators can test the ability of a drug to inhibit alpha-1 receptor activation by testing its ability to reverse PPI drisruption produced by an alpha-1 agonist such a cirazoline. The ability of NT agonists to inhibit alpha-1 receptor activation is what was demonstrated in the disclosure in addition to serotonin-2A receptor inhibition. This was not taught or suggested by the cited references. The ability of NT agonists to inhibit alpha-1 activation in addition to inhibition of activation of serotonin-2A and dopamine makes NT agonists highly auspicious for the treatment of a wider variety of psychiatric symptoms.

Typical and atypical antipsychotics reduce activation of receptors, be it dopamine, serotonin-2A or alpha-1 by binding to those receptors. NT agonists, however are able to reduce activation of these receptors despite the fact that they do not bind any of these receptors. It is thought that they are able to do this by activating NT receptors which in turn shut down the pathways in which dopamine, serotonin and alpha receptors act. Thus NT agonist represent a novel mechanism by which to reduce activation of these receptors.

One major problem with atypical antipsychotics is that they frequently produce weight gain, diabetes and elevated cholesterol. NT agonists, on the other hand, reduce food intake and weight. Thus NT agonists may represent a way to treat many of the psychiatric disorders currently being treated with atypical antipsychotics with much less side effects.

As set forth in the specification, typical and atypical psychotropic drugs act by binding to the dopaminergic receptor (typical) or to the serotonin-2A and

dopaminergic receptor (atypical). NT agonist, however, act by yet a further mechanism and do not bind to either of these receptor, yet are capable of inhibiting serotonin-2A and/or alpha-1 receptor mediated neural function. The present disclosure provides an unrecognized therapeutic drug for the treatment of various psychotic diseases and disorders that is independent of dopaminergic and serotonin-2A receptor mediated activity.

Furthermore, as the specification demonstrates DOI is an agonist of the serotonin-2A receptors not dopamine receptors. Blocking of the serotonin-2 receptor produces therapeutic benefit for a wide variety of psychiatric disorders other than schizophrenia and even for a wider range of symptoms suffered by schizophrenia patients (negative and cognitive symptoms) than blocking of dopamine receptors alone . Blocking of alpha-1 receptors in the presence of blocking serotonin-2A receptors further enhances the ability to treat this wide range of symptoms. The specification and data show that neurotensin agonists such as NT69L and PD149163 reverse the effects of DOI and cirazoline, selective serotonin-2A and alpha-1 receptor agonists, respectively. The ability to block transmission at serotonin 2A and alpha-1 receptors were not known to be a pharmacological properties of neurotensin agonists prior to the studies described in the present application.

The animal model of PPI disruption produced by drugs such as amphetamine or DOI or cirazoline provides researchers information about the pharmacological properties. A drug which reverses PPI disruption by amphetamine, a dopamine receptor agonist, may not reverse PPI disruption by DOI which is a serotonin-2 agonist and vice versa. Similarly with cirazoline, a selective alpha-1 agonist. Regardless of pathophysiology relationship, drug-induced PPI disruption provide a specific in vivo "assay" to obtain knowledge about the specific pharmacological properties of a test drug. This function of the drug induced PPI disruption rat model was a feature underlying the discovery of new, therapeutically relevant, pharmacological properties associated with neurotensin agonists such as NT69L and PD149163.

I. REJECTION UNDER 35 U.S.C. §103

Claims 15-16, 18, 22, 24 and 26 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Hertel et al. (Eur. J. Pharmacol. 422:77-81, 2001), in view of Feifel et al. (Brain Res. 760:80-84, 1997). Applicants respectfully traverse this rejection.

Hertel et al. in combination with Feifel et al. fail to teach or suggest (i) improving symptoms by increasing sensorimotor gating in a subject having a bipolar disease or disorder, an anxiety disease or disorder or a depression disease or disorder (see, e.g., claims 15 and 16); and (ii) fail to teach or sugges any aspect of claim 24.

Hertel et al. and Feifel et al. teach that NT69L reverses amphetamine-induced increase in locomotor activity and amphetamine-induced prepulse inhibition, respectively. As described above, amphetamine produces these effects by stimulation of the dopamine receptor function.. Hertel et al. and Feifel et al. thus teach and suggest that NT69L blocks stimulation at dopamine receptors. However, in contrast, the disclosure demonstrates NT agonist including NT69L and PD149163 block stimulation of 5-HT2A receptors since it blocks PPI disruption by DOI which reduces PPI by activation of 5-HT2A, but not dopamine, receptors.

Nothing in Hertel et al. or Feifel et al. teach or suggest the use of an NT agonist in the treatment of bipolar diseases or disorders, anxiety diseases or disorders or depression disease or disorders. Furthermore, the references when combined do not teach or suggest modulating any of the disease or disorders above as described in claim 24. Nothing in the references teach or suggest a role of NT agonist as putative atypical antipsychotics that modulate serotonin and dopaminergic pathways without interacting with the respective receptors (5HT-2A and D2, respectively). Because Hertel et al. and Feifel et al. recognized only the ability to modulate dopaminergic receptors a biochemical effect that, by itself, has only a limited ability to improve symptoms of psychiatric disorders, namely positive symptoms in schizophrenia, but not the symptom spectrum in other disorders such as bipolar disorder, depression and anxiety. In contrast, modulation of serotonin receptors, by itself or in combination with modulation of dopamine receptors has

been demonstrated to produce improvements in a broad spectrum of psychiatric disorders.

In contrast to Hertel et al, and Feifel et al, the disclosure demonstrates that NT agonist have a broader spectrum of biochemical effects than just inhibition of dopamine receptors, namely that NT agonists modulate serotonin-2A receptors. This discovery demonstrates that NT agonists have a potential to treat a wider range of psychiatric symptoms that previously assumed when they were know only to modulate dopamine receptors.

The Office Action alleges at page 4, paragraph 10, that it would have been obvious to one of skill in the art to modify the use of NT69L for reversing amphetamine induced hyperactivity. However, Applicant respectfully submits that even if such a motivation or modification of the references was suggested the result would only provide the use of NT69L to treat certain symptoms of schizophrenia, namely positive symptoms since only these symptoms are known to be improved by inhibition of dopamine receptors alone. As discussed above, nothing in the cited references suggest treating bipolar diseases or disorders, anxiety diseases or disorders or depression disease or disorders associated with other neurotransmitter pathways such negative symptoms, cognitive deficits associated with schizophrenia. Thus, Hertel et al. combined with Feifel et al. do not teach or suggest bipolar diseases or disorders, anxiety diseases or disorders or depression disease or disorders and thus fail to teach or suggest each and every element of Applicant's claimed invention.

Claims 15-17 and 25 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hertel et al. and Feifel et al. in view of Costa et al. (Eur. J. Pharm. 428:97-103,2001). Applicant respectfully traverses this rejection.

Costa et al. is combined with Hertel et al. and Feifel et al. to allegedly provide the element of treating a subject with SR48692 and SR142948. Applicant submits that the piecing together of elements of the disclosure fails to view the invention as a whole.

Taken as a whole, the disclosure demonstrates that NT agonist provide a class of novel drugs useful for a broader spectrum of diseases and symptoms

disorder that could not otherwise be treated with therapeutics that modulate dopaminergic receptor activation alone (as allegedly taught by the cited references.). Taken as a whole, the combination of Hertel et al., Feifel et al. and Costa et al. fail to teach or suggest the treatment of bipolar diseases or disorders, anxiety diseases or disorders or depression disease or disorders.

At the root of a prima facie obviousness rejection is the fact that the elements set forth in the claims must be taught by the reference or references when combined. The combination of Hertel et al., Feifel et al. and Costa et al. do not teach or suggest each and every element of the claimed invention and thus fails to provide a prima facie case of obviousness.

For, at least, the foregoing reasons the claims submitted herewith are non-obvious over the references either alone or in combination.

For at least the foregoing, the Applicant submits that the claimed invention is patentable and request reconsideration and notice of such allowable subject matter.

The Director is authorized to charge any required fee or credit any overpayment to Deposit Account Number 50-4586, please reference the attorney docket number above.

The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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Date: April 13, 2009

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